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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/079,609	02/21/2002	Stefan Kochanek	50125/020002	7269
21559	7590	11/15/2005		
CLARK & ELBING LLP 101 FEDERAL STREET BOSTON, MA 02110			EXAMINER WHITEMAN, BRIAN A	
			ART UNIT	PAPER NUMBER

1635

DATE MAILED: 11/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No.	Applicant(s)	
	10/079,609	KOCHANЕК ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 27 October 2005.
- 2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-25 is/are pending in the application.
- 4a) Of the above claim(s) 7,8,11-20 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-6,9,10,21-25 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                        | 4) <input checked="" type="checkbox"/> Interview Summary (PTO-413)          |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)    | Paper No(s)/Mail Date. <u>10/31/05</u> .                                    |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____.  | 6) <input type="checkbox"/> Other: _____.                                   |

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## **DETAILED ACTION**

### **Final Rejection**

Claims 1-25 are pending.

Applicant's traversal and the amendment to claims 5, 9, 10, 22, and 25 filed on 10/27/05 are acknowledged and considered by the examiner.

### ***Election/Restrictions***

An iris pigment epithelial cell in claim 2 and claims 7, 8, and 11-20 and an anti-angiogenetic factor, anti-oxidative factor, lysosomal factor, vasodilating factor in claim 3 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and GDNF, NGF, BDNF, CNTF, bFGF and neurotrophin 3, 4-5 in claim 3 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11/20/03.

### ***Information Disclosure Statement***

Applicant's request that examiner consider and initial the IDS mailed on 10/16/02. An IDS was not filed 10/16/02, but there was an IDS filed on 10/21/02. The IDS filed on 10/21/02 was already initialed and considered by the examiner. During a telephonic interview with applicant's representative on 10/31/05, the representative acknowledged that the IDS filed on 10/21/02 was the IDS mailed by applicant on 10/16/02. See interview summary 10/31/05.

### *Claim Objections*

Claim 2 is objected to because of the following informalities: claim 2 embraces non-elected embodiments (iris pigment epithelium cell). Appropriate correction is required.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The intended use of the genetically modified pigment cell of the eye (e.g., in a fixed assemblage of cells) in the instant claim 6 does not have patentable weight for prior art rejections. See MPEP 2111.02. An intended use does not provide a structural difference between the claimed invention and the prior art.

The intended use of the genetically modified pigment cell of the eye (e.g., medicament or diagnostic aid) in the instant claim 21 does not have patentable weight for prior art rejections. See MPEP 2111.02. An intended use does not provide a structural difference between the claimed invention and the prior art.

The intended use of the genetically modified pigment cell of the eye (e.g., where the cell has been cultivated in the presence of a feeder layer or in serum free-medium) in the instant claims 23 and 24, respectively, does not have patentable weight for prior art rejections. See MPEP 2111.02. An intended use does not provide a structural difference between the claimed invention and the prior art.

Claims 1, 2, 4-6, 9, and 21-24 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Reichel et al. (Ophthalmology, 96:570-577, 1999 (English translation of article in German provided by applicants on a PTO-1449, pages 1-15)).

Reichel teaches that after subretinal injection of adenovirus, a very efficient transduction of the RPE can be recognized and gene expression is observed in RPE (page 7). Reichel teaches that a cDNA controlled by CMV promoter was administered to RPE using an adenovirus (pages 11 and 14-15). The RPE cell would read on the limitation in instant claim 5 because one of

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ordinary skill in the art would consider any endogenous protein (e.g., RPE65) produced by the cell to be therapeutic since the protein is required by the cell to function. The RPE cell would read on the limitation in instant claim 22 because one of ordinary skill in the art would understand that in order to produce an endogenous protein an endogenous DNA sequence would be transcribed into a RNA sequence than translated into a protein. Reichel teaches a retina comprising encapsidated adenovirus mini chromosomes (EAMs), wherein the adenovirus has a gene regulated by a promoter (pages 3, 7-8, and 10). The adenovirus lacks all viral genes and the immunogenicity of the vector is reduced (page 8). In addition, the EAMs can be purified to high titers and have a packaging size of 36kb (page 8). Accordingly, in view of the prior art represented by Reichel, one of ordinary skill in the art would have had sufficient motivation to produce RPE cells comprising an adenovirus comprising a nucleic acid operatively linked to a promoter, in particular recombinant adenovirus comprising no adenoviral coding DNA sequences, with a reasonable expectation of success.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made, namely to produce a RPE cell comprising EAMs comprising a nucleic acid operatively linked to a promoter. One of ordinary skill in the art would have been motivated to produce a RPE cell comprising said EAM because Reichel teaches that EAMs are an improvement over adenoviral vectors having adenoviral coding DNA sequence because EAMs have reduced immunogenicity compared to an adenovirus having adenoviral coding DNA sequences; EAMS also can deliver larger nucleic acids compared to an adenovirus having adenoviral coding DNA sequences; and EAMs can be used to deliver the nucleic acid to the cell.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made, namely to use EAMs in a method for producing a RPE cell comprising EAMs comprising a nucleic acid operatively linked to a promoter. One of ordinary skill in the art would have been motivated to use EAMs to produce said RPE cell because Reichel teaches that EAMs are an improvement over adenoviral vectors with adenoviral coding DNA sequences and EAMs can be used to deliver the nucleic acid to the cell.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 10/27/05 have been fully considered but they are not persuasive.

Applicant argues that Reichel teaches away from the claimed invention because Reichel does not disclose a vector for long-term expression in the pigment epithelium of the eye. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., long-term) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). This is the case here. There are no structural elements recited in the claims to support the basis of applicant's argument directed to Reichel not teaching using the adenovirus as a long-term expression vector. In addition, instant claims 1-8 and 21-24 are directed to product claims and the intended use of the product does not have patentable weight under a prior art rejection. See MPEP 2111.02.

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In response to applicant's argument that gene expression from EAMs following subretinal injection of the EAM described by Reichel was detected exclusively in the neuronal part of the retina and not in the retinal pigment epithelium (See Kumar-Singh and applicant's specification page 4, line 11- page, line 2). The claims read on in vitro and in vivo cells. In view of the prior art, one of ordinary skill in the art would reasonably expect success when transfecting in vitro RPE cells with EAM. The examiner acknowledges that the specification asserts that subretinal administration of EAM taught by Kumar-Singh (supra) did not result in gene expression of RPE. However, the examiner reviewed the article and could not find support in Kumar-Singh to support applicant's assertion that Kumar-Singh teaches that subretinal administration of EAM did not result in gene expression in RPE. The prior art indicates that adenoviral vectors can successfully transfect RPE cells and express an exogenous gene in RPE cells (See page 7 and 9 of English translation of Reichel). EAMs are adenoviral vectors and when the reference relied on expressly anticipates or makes obvious all of the elements of the claimed invention, the reference is presumed to be operable. Once such a reference is found, the burden is on applicant to provide facts rebutting the presumption of operability. In re Sasse, 629 F.2d 675, 207 USPQ 107 (CCPA 1980). See also MPEP § 716.07. See In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). Thus, in view of the prior art, one of ordinary skill in the art would have a reasonable expectation of success of using an EAM to transfect and express an exogenous gene in RPE cells.

Claims 1 and 3 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Reichel et al. (Ophthalmology, 96:570-577, 1999) as applied to claims 1, 2, 4-6, 9, and 21-24 above, and further in view of Kovesdi (US 2003/0045498).

Reichel teaches that RPE are available for ex vivo gene transfer (page 4). However, Reichel does not specifically teach genetically modified retinal pigment epithelial cell (RPE) of the eye with an adenoviral vector comprising a nucleic acid encoding PEDF operatively linked to a promoter.

However, at the time the invention was made, Kovesdi teaches administering an adenoviral vector comprising a nucleic acid sequence encoding a pigment epithelium-derived factor (PEDF) to retinal pigment epithelial cells (abstract, pages 2, 3, 4, 6, 15, and 16). Kovesdi teaches that the adenoviral vector is deficient in genes essential for viral replication such that the vector can accept large inserts of exogenous DNA (pages 4-5). Kovesdi teaches that any promoter can be used in the vector, e.g., constitutive, regulatable, tissue-specific (pages 6-7). Kovesdi teaches a pharmaceutical composition comprising the vector and using the vector to study treatment of ocular disorders (pages 12 and 13).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Reichel taken with Kovesdi to produce a genetically modified pigment epithelial cell comprising an adenoviral vector comprising a nucleic acid encoding PEDF operatively linked to a promoter, wherein the vector comprises no adenoviral coding DNA sequence. One of ordinary skill in the art would have been motivated to produce the cell to study the treatment of ocular disorders by expressing PEDF. In addition, one ordinary skill in the art would have been motivated to use EAM instead of the adenoviral vector

taught by Kovesdi for producing the cell because EAM have reduced immunogenicity compared to adenoviral vector having adenoviral DNA coding sequence because it does not contain adenoviral coding DNA sequences and would result in an increase in PEDF expression in the cell because the immune response would not interfere with EAM before EAM transfects the cell and expresses the PEDF.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 10/27/05 have been fully considered but they are not persuasive for the reason set forth under the prior 103(a) rejection.

Claims 1 and 10 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Reichel et al. (Ophtalmologe, 96:570-577, 1999) as applied to claims 1, 2, 4-6, 9, and 21-24 above, and further in view of Tezel et al., (Exp. Eye Res. (1998) 66, 807-815).

Reichel teaches that RPE are available for ex vivo gene transfer because of the possibility of culturing (page 4). However, Reichel does not specifically teach culturing the genetically modified retinal pigment epithelial cell (RPE) of the eye in serum-free media.

However, at the time the invention was made, Tezel teaches that serum-free media can be used for culturing RPE cells (page 807). Tezel further teaches culturing the cells onto tissue-culture plastic pre-coated with bovine corneal endothelial extracellular matrix (page 807). Tezel teaches, "The presence or absence of serum-derived hormones, cytokines, carrier proteins, cell attachment factors and cell spreading factors can have a profound effect on the behavior of RPE cells in tissue culture and may mask the specific effects of a particular exogenous cytokine(s) on

RPE. For these reasons, several researchers have cultured RPE with reduced or not serum supplementation (page 807).” Tezel teaches, “This is particularly important for RPE, because RPE cells exhibit phenotypic heterogeneity (page 812).”

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Reichel taken with Tezel to culture genetically modified retinal pigment epithelial cells in serum-free media. One of ordinary skill in the art would have been motivated to culture the RPE cells in serum-free media because Tezel teaches that culturing RPE cells in serum-free medium avoids the effect of hormone, cytokines, carrier proteins, cell attachment factors and cell spreading factors on the behavior of RPE cells in tissue culture.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 10/27/05 have been fully considered but they are not persuasive for the reason set forth under the prior 103(a) rejection.

Claims 1 and 10 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Reichel et al. (Opthalmologe, 96:570-577, 1999) as applied to claims 1, 2, 4-6, 9, and 21-24 above, and further in view of Funk et al., (US 6,667,176) and Williams et al., (Nature, 1988, 336:684-7).

Reichel teaches that RPE are available for ex vivo gene transfer because of the possibility of culturing (page 4). However, Reichel does not specifically teach culturing the genetically modified retinal pigment epithelial (RPE) cell of the eye in the presence of a feeder layer.

However, at the time the invention was made, Williams teaches that maintenance of stem-cell phenotype *in vitro* requires the presence of a feeder layer (page 684).

In addition, at the time the invention was made, Funk teaches that RPE cells are progenitor cells (column 17, lines 34-57).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Reichel taken with Williams and Funk to culture genetically modified retinal pigment epithelial cells in the presence of a feeder layer. One of ordinary skill in the art would have been motivated to culture the RPE cells in the presence of a feeder layer because Williams teaches that culturing stem cells in the presence of a feeder layer maintains stem-cell phenotype *in vitro* and Funk teaches that RPE cells are progenitor cells.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 10/27/05 have been fully considered but they are not persuasive for the reason set forth under the prior 103(a) rejection:

Claims 1 and 25 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Reichel et al. (Opthalmologe, 96:570-577, 1999) as applied to claims 1, 2, 4-6, 9, and 21-24 above, and further in view of Funk et al., (US 6,667,176), Williams et al., (Nature, 1988, 336:684-7) and Tezel et al., (Exp. Eye Res. (1998) 66, 807-815).

Reichel teaches that RPE are available for ex vivo gene transfer because of the possibility of culturing (page 4). However, Reichel does not specifically teach culturing the genetically

modified retinal pigment epithelial (RPE) cell of the eye in a serum-free medium and in the presence of a feeder layer.

However, at the time the invention was made, Williams teaches that maintenance of stem-cell phenotype *in vitro* requires the presence of a feeder layer (page 684). In addition, Funk teaches that RPE cells are progenitor cells (column 17, lines 34-57).

Furthermore, at the time the invention was made, Tezel teaches that serum-free media can be used for culturing RPE cells (page 807). Tezel further teaches culturing the cells onto tissue-culture plastic pre-coated with bovine corneal endothelial extracellular matrix (page 807). Tezel teaches, "The presence or absence of serum-derived hormones, cytokines, carrier proteins, cell attachment factors and cell spreading factors can have a profound effect on the behavior of RPE cells in tissue culture and may mask the specific effects of a particular exogenous cytokine(s) on RPE. For these reasons, several researchers have cultured RPE with reduced or not serum supplementation (page 807)." Tezel further teaches, "This is particularly important for RPE, because RPE cells exhibit phenotypic heterogeneity (page 812)."

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Reichel taken with Williams and Funk in further view of Tezel to culture genetically modified retinal pigment epithelial cells in serum-free medium and in the presence of a feeder layer. One of ordinary skill in the art would have been motivated to culture the RPE cells in the presence of a feeder layer because Williams teaches that culturing stem cells in the presence of a feeder layer maintains stem-cell phenotype *in vitro* and Funk teaches that RPE cells are progenitor cells. In addition, one of ordinary skill in the art would have been motivated to use serum-free medium in the method because Tezel

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teaches that culturing RPE cells in serum free medium avoids the effect of hormone, cytokines, carrier proteins, cell attachment factors and cell spreading factors on the behavior of RPE cells in tissue culture.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 10/27/05 have been fully considered but they are not persuasive for the reason set forth under the prior 103(a) rejection.

#### ***Response to Arguments***

Applicant's arguments, see page 7, filed 10/27/05, with respect to 112 second paragraph have been fully considered and are persuasive. The rejection of claims 9, 10, and 25 has been withdrawn.

#### ***Conclusion***

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

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however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764.

The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, acting SPE – Art Unit 1635, can be reached at (571) 272-0811.

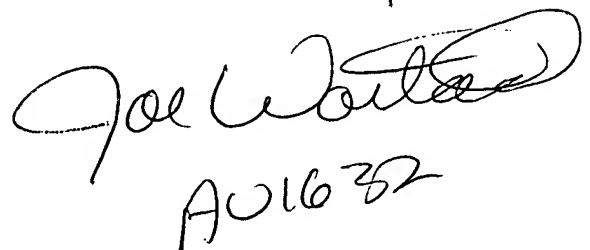
Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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Brian Whiteman  
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